COMBINATORIAL IMMUNOTHERAPY STRATEGIES: MOST GODS THROW DICE, BUT FATE PLAYS CHESS

Immuno-oncology drugs (IODs) are considered as game-changing treatments in oncology, because diseases with once dismal prognosis such as metastatic melanoma or lung cancer now show 3-year survival rates in the 20-40% range. However, it has to be kept in mind that, to date, success stories with immunotherapy are limited to a small subset of lucky individuals in an even smaller subset of cancers. As a consequence, stretching the efficacy of IODs to a larger number of patients with a wider range of cancers is now the main challenge in clinical oncology. Developing combinatorial regimens (i.e., combining the most recent immune checkpoint inhibitors with canonical cytotoxics, targeted therapies, anti-angiogenics or radiation therapy) is currently seen as the most promising strategy to turn once immunologically "cold" tumors into "hot" ones. Standard treatments are expected indeed to harness tumor immunity through a variety of mechanisms, ranging from promoting immunogenic cell death and neo-antigen expression on cancer cells to increasing T lymphocytes infiltration or decreasing Tregs or Myeloid-Derived Suppressive Cells (MDSCs) expression in the tumor micro-environment [1]. Countless combinational trials in a variety of tumor types have thus been initiated over the last few years, and clinical benefit has already been reported (for instance in non-small cell lung cancer when IODs are combined with cytotoxics) [2]. In triple negative breast cancer (TNBC), the TONIC trial (NCT02499367) was the first clinical study to demonstrate how improved clinical outcome observed with nivolumab in patients pre-treated with cytotoxics such as doxorubicin or cisplatin was actually associated with immunomodulating features, such as increases in CD8's and tumor infiltrating lymphocytes (TILs) or in upregulation of a variety immune-related genes implicated in enhanced T cells priming [3]. However, out of the hundreds of trials investigating combinations of immune checkpoint inhibitors with other therapies, many -if not most- of them have failed to yield similar convincing results. For instance, attempts to combine IODs with radiation therapy, metronomic or maximal tolerated dose (MTD) chemotherapy, anti-angiogenics or oral targeted therapies have frequently led to disappointing results in several other settings [4,5].

Of note, the common theme in all of these trials relying on an expected synergism between IODs and other treatments is the apparently complete lack of a rationale when defining

dosing, scheduling and sequencing of the combinations. For instance, concomitant dosing is frequent, as in the Modul trial exploring the combination of anti-PDL1 atezolizumab with standard cytotoxics (i.e., 5-FU, capecitabine) and a canonical anti-angiogenesis agent (i.e., bevacizumab) in metastatic colorectal cancer [6]. Bevacizumab is expected to help T lymphocytes to better infiltrate tumors by diapedesis and to reduce the anti-immunogenic effects of endothelial cells [7], whereas fluoropyrimidine drugs should induce immunogenic cell death and could additionally decrease Tregs expression in the tumor micro-environment [1]. However, all of these theoretical immunomodulating properties are more probably dose-dependent and time-dependent. For instance, acting on the “brake” (i.e., decrease Tregs or MDSCs) or “gas” (i.e., increase T Lymphocytes infiltration or promote immunogenic cell death) pedals with cytotoxics could depend on the chosen dosing, as already suggested by experimental data [1]. Consequently, setting up such complex trials combining three different drugs would probably have required fine tuning to determine the optimal way to best combine treatments to achieve optimal immunomodulating properties and synergism with IODs.

With respect to the high number of possible combinations between different dosing, scheduling and sequencing when combining immune checkpoint inhibitors with several other drugs, empirical designs with concomitant administration at standard dosing are doomed to yield disappointing, if not negative, results, as in the Modul trial. Interestingly, in the TONIC trial, rather than concomitant dosing, all the associated treatments or irradiation were delivered as induction therapy, i.e. two-weeks before nivolumab started [3]. Although not designed to be comparative, this study showed marked differences between treatments, because better clinical outcome was observed in TNBC patients pre-treated with low-dose cisplatin and doxorubicin than in patients treated with low-dose cyclophosphamide or radiation therapy. This suggests that scheduling and/or dosing should probably be further customized depending on the drugs used, to enhance T cell priming and to eventually achieve clinical benefit. Generating biological data as in the TONIC trial certainly helps to better delineate the immunomodulating properties of associated treatments and could help investigators to improve further the modalities of combination, in a trial-and-error fashion. Importantly, mathematical oncology and pharmacometrics could possibly help to narrow down the choices when setting up such combinations, i.e., by extensive *in silico* modeling &

simulation strategies implemented prior to running the actual trials. Several mathematical modeling strategies can be used with varying degrees of complexity, from “black-box” statistical models (e.g. machine learning) to very intricate multiscale models. Whereas machine learning analysis lacks the simulative power to explore the large number of scheduling possibilities, mechanistic models on the other hand have to be parsimoniously tailored to the dimensionality of available clinical data that often remain scarce [8]. Indeed, models aiming at integrating all the biological complexity and multiple interplays when considering tumor immunity are prone to over-parameterization, which in turn may lead to overfitting and lack of predictive power. Parsimonious, semi-mechanistic approaches have already been successfully tested elsewhere to help investigators to design innovative, model-driven clinical trials with cytotoxics or targeted therapies [9, 10], including to define optimal combination modalities [11]. Such strategies start to emerge as well in the field of combinatorial regimen with IODs. For instance, a simple model calculating an immunologically effective dose (IED) has been already proposed to compute radiation therapy fractionation schemes with immunogenicity as a readout [12]. Using this approach, optimal timing when administrating nivolumab and ipilimumab with respect to associated hypofractionated radiotherapy is now currently tested at the bedside as part of a phase-I study in previously treated, advanced non-small cell lung cancer(NCT03509584). This example shows how mathematical oncology could be used as a decision-making tool when setting up combinatorial studies, to shift from empirical designs to model-informed clinical trials. Time has probably come to stop throwing dice, especially when cancer plays chess.

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